REMARKS

As a preliminary matter, the Action was mailed on October 2, 2002. Applicants submitted a Notice of Appeal on April 2, 2003 in conjunction with a REPLY, containing amendments and remarks, responding to the Action. Applicants also submitted a SUPPLEMENTAL REPLY TO OFFICE ACTION on April 3, 2003 with amendments and remarks. On May 9, 2003, Applicants additionally submitted a SUPPLEMENTAL REPLY enclosing a Combined Declaration and Power of Attorney. On May 7, 2003, an Advisory Action was sent by the Examiner stating that the proposed amendments would not be entered. On Applicants' information and belief, neither of the amendments filed after the Action, nor the Combined Declaration and Power of Attorney were entered.

Applicants submit herewith a Request for Continued Examination (RCE) of the Application and request entry of the enclosed amendments, which address the objections and rejections of the Final Office Action. Pursuant to 37 C.F.R. 1.114(d), since this RCE is filed after appeal, but prior to a decision on appeal, Applicants respectfully request withdrawal of the appeal and reopening of prosecution of the application before the Examiner.

Applicants request entry and acceptance of the SUPPLEMENTAL REPLY enclosing the Combined Declaration and Power of Attorney, as filed on May 9, 2003. Applicants will re-submit the Combined Declaration and Power of Attorney, at the Examiner's request.

Applicants request NON-ENTRY of Applicants' REPLY mailed April 2, 2003 and the amendments presented therein and Applicants' SUPPLEMENTAL REPLY mailed April 3, 2003 and the amendments presented therein.

Drawings

With regard to item number 3 on page 2 of the Action, Applicants submit herewith formal drawings which Applicants believe to be compliance with 37 CFR 1.84. Please do not

hesitate to contact the undersigned should the Examiner find any further defects or have any questions with respect to the drawings.

Specification

With regard to item number 4A on page 3 of the Action, Applicants hereby amend the first line of the specification to update the status of the priority documents to refer to the Provisional Application. Applicants hereby amend the specification to correct obvious typographic errors. Those errors would be readily apparent to a person of ordinary skill in the art. No new matter is added by these amendments.

Declaration

With regard to item 4B in the Action, and as discussed above, Applicants respectfully request that the Declaration filed with the May 9, 2003 SUPPLEMENTAL REPLY be entered and acceptance of the Declaration submitted therewith. By this, Applicants believe that the Examiner's requirement that Applicants submit a new Declaration is fully addressed. In addition, please find enclosed a copy of the current Power of Attorney sent to the PTO on October 21, 2001 by facsimile to RightFax – After Final ((703) 872-9307). Applicants were later informed by the Examiner that the document should have been faxed to the "non-final" RightFax number, (703) 872-9306, but since Applicants received a receipt from the PTO, no second facsimile was sent to the 9306 extension to avoid confusion.

Claims

Claims 1-42 were submitted with the originally filed application on August 24, 1999. On August 29, 2000 the Examiner restricted the claims into 12 groups. Groups I and II, encompassing claims 1-15, were rejoined by the Examiner in the Office Action of July 17, 2001. Groups I and II were elected for examination, with claims 16-42 withdrawn. In the Office Action response of January 16, 2002, claims 1-15 were cancelled and new claims 43-57 were

submitted. Claims 58 and 59 were submitted in the Supplemental Amendment of January 25, 2002. As indicated above, additional amendments were submitted in response to the Action in the REPLY mailed on April 2, 2003 and in the SUPPLEMENTAL REPLY TO OFFICE ACTION mailed on April 3, 2003. Those after-final amendments were not entered. As indicated above, Applicants respectfully request that the amendments presented in the REPLY mailed on April 2, 2003 and the SUPPLEMENTAL REPLY TO OFFICE ACTION mailed on April 3, 2003 remain un-entered in favor of the amendments to the claims presented herein.

Applicants also respectfully request that claims 1-50 and 52-59 be cancelled. Claim 51 has been rewritten as per suggestion by the Examiner and is believed to be allowable. New claims 60-78 have been added for examination. The newly claimed material is described in the specification and figures as filed with no new matter added by these amendments or claims. Objections and rejections raised in the Action will be addressed in detail below.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 43-50 and 52-59 under 35 U.S.C. § 112, first paragraph. The Examiner stated that the specification "does not reasonably provide enablement for the broader recitation of reducing any immune mediated damage to a cell, tissue, or organ" and that the "specification does not enable any person skilled in the art . . . to make the invention commensurate in the scope with these claims."

Applicants respectfully disagree with the Examiner. Without intending to relinquish any scope of claims 43-50 and 52-59, however, Applicants respectfully request that the Examiner cancel claims 43-50 and 52-59 in favor of new claims 60-78. In view of these amendments and for the reasons set forth below, Applicants respectfully request reconsideration of this enablement rejection.

The Examiner has indicated in paragraph 6, page 3 of the Final Office Action, that the specification is enabling "for a method for reducing immune mediated damage to cells, tissues

or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of HSP47 (SEQ ID NO:6) or a fragment thereof that consists of AVSAEQLR (SEQ ID NO:3)." Claim 51 has been rewritten in independent form as per the suggestion of the Examiner (paragraph 7 of Final Office Action) to place it in proper form for allowance.

Additionally, the Examiner asserts that the "instant specification provides enablement only for a method comprising HSP47 polypeptide (SEQ ID NO:6), and a fragment of an HSP47 polypeptide consisting of the sequence AVLSAEQLR (SEQ ID NO:3), and compositions thereof, in reducing immune-mediated damage by CIK cells. The instant specification does not provide sufficient direction that said HSP47 peptides protect against immune-mediated damage by other immune cell[s] (sic)." The Examiner, however, states that "the literature is silent with respect to the ability of HSP47 peptides to reduce immune mediated damage by cells other than CIK." The Examiner then states, "In view of the diversity of immune effector cells, it would require undue experimentation for one of skill to predict which immune effector cells, other than CIK cells, would be effected by the recited HSP47 peptides without further guidance and direction from the instant specification."

First, Applicants respectfully disagree that specification provides enablement only for a method utilizing compounds comprising SEQ ID NO:6 and SEQ ID NO:3. The specification provides other enabling embodiments, for example but not limited to, the fusion protein of human Hsp47 with N-terminally tagged glutathione-S-transferase (Gst), Hsp47 with leader sequences added on (SEQ ID NOS:19-20), and truncated forms of Hsp47 (*see* pp. 27-28 of originally filed application and Figures 9, 11, 12, and 15). These particular embodiments were also shown to have immunoprotective effect. Conservatively substituted versions of the composition are described, for example, on page 7, and the art-recognized conservative amino acid substitutions included in those versions are described in Table 1 on page 9. Applicants describe fully how to make and use the claimed embodiments, The examples, in combination

both with the teachings in the art at the time of filing of the present application with regard to conservative amino acid substitutions and with the limited number of these substitutions claimed in the present application, render those claimed peptides enabled.

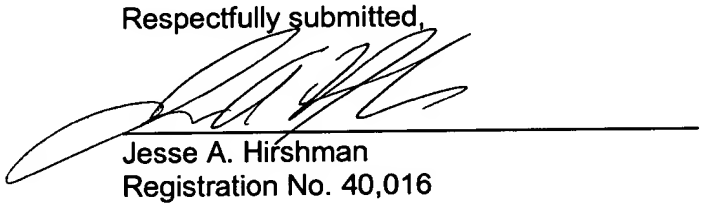
Secondly, Applicants respectfully disagree with the Examiner's argument that the specification does not provide sufficient direction with regard to HSP47 peptides protecting against immune-mediated damage by other immune cells. There is nothing in the literature that contradicts the notion that HSP47 peptides reduce immune mediated damage by cells other than CIK. The specification also provides embodiments demonstrating immunoprotective effect without the administration of CIK cells. For example, the murine bone marrow transplant studies described on page 55 of the specification and in Figure 15 involved no administration of CIK cells. In these studies, 10 mice were irradiated with each receiving a transplant of bone marrow and spleen cells from mice of a different strain. Five experimental mice received Hsp47-Gst fusion protein, whereas five control mice received no fusion protein. Four of five control mice died over the four week observation period, whereas all five experimental mice survived.

Production of CIK cells is described in Example 1, beginning on page 34 of the specification. The murine bone marrow transplant study described above does not involve that population of CIK cells, at least CIK cells as described in Example 1. It is clear that immune-mediated damage by other immune cells was prevented in this experiment because bone marrow transplantation comprises transplant of all lineages, both in peripheral blood system and in the bone marrow. Thus cells of lymphoid, erythroid, myeloid and other lineages are included. Undue Experimentation to identify which particular lineage of cells causes immune-mediated damage is not necessary in order to enable the invention because Applicants have demonstrated that immune-mediated damage is prevented by exposure of the subject compositions. Although Applicants have gone far in demonstrating that CIK cells can be used

to demonstrate immune-mediated damage, the recitation of "CIK cells" is not necessary in light of the above-referenced *in vivo* studies.

Applicants believe that the amended claim and new claims are in proper form for allowance. Applicants respectfully request allowance of claims 51, and 60-78. Applicants also request that the Examiner call Judith S. H. Hom to discuss any additional questions or concerns with respect to the above-referenced patent application.

Respectfully submitted,



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